

## The emerging landscape of reimbursement of regenerative medicine products in the UK: publications, policies and politics

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## **The emerging landscape of reimbursement of regenerative medicine products in the UK: publications, policies and politics**

### **Structured Abstract**

#### **Aims**

This paper aims to map the trends and analyse key institutional dynamics that are constituting the policies for reimbursement of Regenerative Medicine (RM), especially in the UK.

#### **Materials & Methods**

Two quantitative publications studies using Google Scholar and a qualitative study based on a larger study of 43 semi- structured interviews.

#### **Results**

Reimbursement has been a growing topic of publications specific to RM and independent from orphan drugs. Risk- sharing schemes receive attention amongst others for dealing with RM reimbursement. Trade organisations have been especially involved on RM reimbursement issues and have proposed solutions.

#### **Conclusion**

The policy and institutional landscape of reimbursement studies in RM is a highly variegated and conflictual one and in its infancy.

### **Keywords**

Reimbursement, regenerative medicine, valuation, publications, trade organisations, orphan drugs, risk- sharing agreements

### **I- Introduction**

Trends in the production of strategic visions of the real-world application of new sciences and technologies and in the production of knowledge in emerging sectors provide important signals for participants striving to develop innovative products and processes. In 2015, based on PubMed analysis, Bayon and al. showed regenerative medicine (RM) to be a very active field, with more than 12, 000 publications on RM and Tissue Engineering between 2012 and 2015 [1]. The question of RM reimbursement, payment or provision of the therapy, is emerging as one of its key issues.

On the one hand, the high cost and low evidence of long- term cost-effectiveness of RM are the most recognised problems regarding RM reimbursement. However, this is not specific to RM having been a prominent issue notably for orphan drugs [2]. Orphan drug is a legal statute attributed to medicines for rare diseases according to similar criteria in Europe, the USA and Japan. This legal status provides several incentives to support the development of drugs for severe disease affecting a small number of people. It is believed that companies would not develop these drugs due to lack of commercial viability otherwise. When RM based products are classified as medicines, they could be qualified as orphan drugs, with the consequent benefits. In Europe, this is in addition to the incentives provided to Advanced Therapy Medicinal Products (ATMPs), defined as gene and cell therapies, tissue engineering, and their combination with medical devices. On the other hand, in a context of limited health resources, managed entry agreements have emerged between producers and payers to manage budget impact and uncertainty regarding relative effectiveness [3]. One type of such agreements is to share the financial risks between the producers and the payers, for example reimbursement being completed annually according to the performance of the product. These 'risk- sharing' agreements have attracted a great deal of interest [4],

are already quite widely used in Italy though with mixed financial success [5], and could be a solution more widely for introducing high cost drugs, especially for RM where outcomes uncertainties are high. Risk-sharing and other managed entry schemes are one focus in recent publications about reimbursement in the RM field, contributing to the technical and political debate that is negotiating RM's wider adoption into health systems.

Publications can be regarded as providing a data resource for describing the characteristics of emerging fields. This applies both to 'external' features that can be used to 'map' an innovation landscape, such as authors, disciplinary affiliations, geographical locations, publication formats, and intended audiences as well to the 'internal' content, discourse and issues raised or not raised in those publications. Published documents are thus performative [6, 7], in other words they not only 'say' things but they also 'do' actions. They embody stakeholders' actions that play a role in defining the contours of a field, its rules of engagement, its materials, its procedures and its participants. Mapping of publications in emerging domains is valuable for stakeholders, including both producers or investors seeking market signals and analysts seeking to target their own analyses in context for publication (e.g.[8]). This paper addresses both such audiences.

Drawing on these approaches, we can address questions of how the potential real-world adoption of RM techniques in healthcare delivery is being envisaged and what knowledge is being brought to bear on it. In a similar vein to Chilvers [9], we can ask questions such as: Who are the leading voices of RM valuation: are the authors of RM reimbursement publications independent analysts, clinical promoters, industry intermediaries, business consultants, innovation catalysts, or others? What clinical and policy spaces are they locating themselves in, oriented to what audiences? At what stage of development is the debate on this topic? Which aspects of the valuation of RM and its reimbursement possibilities do they highlight and downplay?

In the case examined here a range of institutional stakeholders are mobilising their ambitions, expectations, knowledge and methodologies attempting to promote, regulate or otherwise steer RM through policies and scenarios for their valuation and payment. 'Valuation studies' address how actors are engaged in 'performing markets' and are 'examining the multiplicity and disputability of valuation practices, metrics and processes' [10]. Hence a study of stakeholders' positions and diverging values on reimbursement in RM can contribute to understanding the current trends in its evolving landscape and the forces driving the translation of RM – by focusing on the healthcare adoption end of this process.

Guided by this approach, and based on three complementary studies, this paper aims to map the landscape and analyse key institutional dynamics and methodological proposals that are constituting the emerging policies for reimbursement of RM, especially in the UK. The three studies comprise two studies of the publications landscape, one overarching and one more specific, combined with one in-depth study of the most contested aspects of the RM reimbursement debate. Thus the publication studies describe the emerging *forms* and sites of RM reimbursement analysis, while the in-depth (interview-based) study presents the most crucial *content* of the conflictual debates in the field.

## II- Methodology and Results

In this section, we present the methods/results of each of the three complementary studies. We undertook two quantitative studies of publications using Google Scholar and a qualitative study based on interviews.

The time periods the publication searches covered are 2015 and/or 2016. Practically, these were the most recent periods available at the time of our study. Scientifically, the question of RM reimbursement emerged as a prominent issue from 2015. Hence, our systematic searches do not cover earlier publications, although a few relevant publications previous to 2015 are referred to in our discussion.

Google Scholar (GS) was chosen as most relevant for the purposes of this research, following review of options [11,12,13,14]. GS is interdisciplinary and met our supposition that publications on RM reimbursement will be found in various fields of research, and probably more in Social and Human Sciences (SHS) or economics. GS also is not confined to peer-reviewed articles, and it is free to use and thus accessible beyond academia. We supposed transparency and thus wider accessibility are key aspects of RM's reimbursement politics. However, GS also has many limitations, notably it is not as comprehensive or precise as other search interfaces. Therefore, our set of selected articles includes both very detailed publications on RM reimbursement as well as others where it is referred to without being the main focus. Therefore, our results are broadly indicative rather than definitive. We present the results of the three studies below.

### **1) Reimbursement topics in the publications landscape of RM**

For the first study, GS has been used for systematic searches to identify trends in RM publications (referring here to every publication whatever the format is: journals, book, Doctoral dissertation...) during 6 months from January 2016 to July 2016. The full search strategy is available from supplementary file 1. In summary, the following keywords were used: "regenerative medicine" OR "advanced therapy" OR "gene therapy" OR "cell therapy" OR "tissue engineered product" OR "innovative therapies" (that we call "regenerative medicine based products": RMPs), combined with and without the word "UK", and with combinations including or excluding "reimbursement", "risk-sharing", and "orphan drugs". The names of different countries were also included: UK, France, Germany, Japan, South Korea, USA (United States). Various adjustments such as averaging of results over 6 monthly periods were made to allow for GS's performance (Supplementary file 1). New systematic researches were added in February 2016 or in March 2016. (Where averages have been calculated over 6 months or over 5 months instead of 7 months, they are respectively marked with a single (6 months average marked\*) or a double (5 months average marked\*\*) star, in the tables presented). The results are integrated in an Excel table (Supplementary file 2).

This analysis addressed questions including: Is the question of reimbursement prominent among RM publications generally? Is reimbursement discussed to similar

extents in the countries that are the most active in the RM field? Is RM reimbursement specifically considered compared to other expensive medicinal products, especially orphan drugs? Is risk-sharing the most discussed managed entry reimbursement option? The results of our analysis are below.

First, reimbursement of RMPs has been a growing topic of publications between 2015 and 2016, even excluding orphan drugs. Publications on reimbursement/risk- sharing were more numerous in the first six months of 2016 than in the whole year 2015. However, reimbursement/risk- sharing is not a very prominent primary topic, judged by use of these terms explicitly in publications' titles. This is even more true for the UK, as there was no publication including these terms in UK-origin titles.

However, when including orphan drugs the picture changes. Risk- sharing is associated with orphan drugs in more publications (there were generally more than twice as many publications when orphan drugs was included associated with risk sharing. This difference was smaller when orphan drugs was associated with reimbursement as a general term. (Table 1)

Table 1: Publications on reimbursement/Risk sharing, link with orphan drugs

Anywhere	No time limit	Since 2012	Since 2015	Since 2016
Reimbursement excluding orphan drugs	8688*	2537*	973*	373*
Reimbursement including orphan drugs	11643	3807	1378**	517**
Risk Sharing excluding orphan drugs	326*	123*	39*	17*
Risk Sharing including orphan drugs	676	318	105*	38**

However, reimbursement and risk- sharing also appeared as independent topics for RM, shown by publications with 'orphan drugs' excluded from the search terms (See Table 1 and supplementary file 2) although there were fewer publications on RM risk- sharing than on RM reimbursement generally. Thus, the orphan drug focus is greater than that on RMPs, though the latter is attracting an independent set of publications, both on reimbursement generally and risk-sharing in particular.

Finally, regarding the 2015 publications related to reimbursement of RMPs, the UK had the fifth most references (183 results) behind the USA (416 results), Japan (239 results) and Germany (237), close to France (188 results) and before South Korea (56). However, it should be noted that, given GS limitations, these countries could be mentioned in the publications data or as countries of affiliation of the authors (Table 2).

Table 2: 2015 publications related to reimbursement of RMPs per country

	UK	France	Germany	Japan	South Korea	United States
Reimbursement Anywhere Year 2015	183	188*	237*	239*	56*	416*

Thus, UK RM reimbursement is a recent and growing topic of publications, and it appears less developed than in the USA, Japan, Germany, and France, both related to

and independent from orphan drugs, and not only linked to risk- sharing agreements as a main policy option.

## 2) Profiling political characteristics of the RM reimbursement publications landscape

The second study is based on a deeper quantitative analysis of targeted publications identified from the first study. Out of 182 publications found in February 2015, 5 appear twice and 127 have been excluded following inspection as being out of our scope. Thus, our working material is based on 50 publications in 2015. These 50 publications have been classified in different Excel tables to distinguish the various research fields they come from for each type of publications: Journals, books chapters, books, thesis and other types of publications see Supplementary file 3).

This analysis addressed questions including: In which types (journals, book chapters, books, thesis or other kinds of publications) of publications is reimbursement of RM considered? (We hypothesise that books and theses are less accessible than journals for most stakeholders in the field). In which field of research (clinical, SHS, economics, public health, business, other) is reimbursement of RM considered? In which clinical areas is reimbursement of RM considered? Are there dominant journals? Is reimbursement of RM considered by few publishers or many? What is the UK position and authorship in these publications?

Our analysis shows that publications related to RM reimbursement are mainly found in journals (74%; N= 37/50), especially in public health (100%; N= 4/4), clinical (95.7%; N=22/23) and economics (75%; N= 3/4), showing the predominance of the journal format in these disciplines. Nevertheless, a sizeable proportion appears in other formats and so may be less accessible. In addition, the sharing of publications between journals, books' chapters, books, doctoral dissertations, and other types of publications is much more balanced in SHS and business fields. The clinical and economic areas have a similar sharing of publications types regarding RM reimbursement: mainly journals (95.7 % for the clinical area and 75% for the economics area) and few in book chapters (4.3 % (N= 1/23) for the clinical area and 25% (N= 1/4) for the economics area). In the public health area 100% (N= 4/4) publications on RM reimbursement are in journals. On the other hand, the business discipline is an exception, with no publication in journals and more equally represented (together with the SHS area) across other formats of publications (Table 3), suggesting that this discipline may be a less visible area of the landscape

**Table 3: Different types of publication formats by discipline**

	Clinical	SHS	Economics	Public Health	Business	Total
Journals	22 95,7%	8 57,1%	3 75%	4 100%	0 0%	37 74,0%
Book Chapters	1 4,3%	2 14,3%	1 25%	0 0%	2 40%	6 12,0%
Books	0 0%	1 0,1%	0 0%	0 0%	1 20,0%	2 4,0%
Doctoral Dissertations	0 0%	3 21,4%	0 0%	0 0%	1 20,0%	4 8,0%

Other	0 0%	0 0%	0 0%	0 0%	1 20%	1 2,0%
Total Publications	23 100%	14 100%	4 100%	4 100%	5 100%	N= 50 100%

Moreover, one of our first suppositions has been verified in that publications related to RM reimbursement are found in a range of different fields of research. However, the dominant field is not SHS (28.0%; N= 14/50) nor economics (8.0%; N= 4/50) but is clinical (46.0%; N= 23/50); public health being more or less equivalent to economics (8.0%; N= 4/50) and business (10.0%; N= 5/50). Thus, the questions of RM reimbursement are being formulated mainly in clinical and SHS disciplinary publications (Table 4).

**Table 4: Range of different publications subject areas/types**

Clinical	SHS	Economics	Public Health	Business	Total
23	14	4	4	5	N= 50
46,0%	28,0%	8,0%	8,0%	10,0%	N= 100%

Of the clinical articles, most were in generalist medical journals (45.5%; N= 10/22). When specific disease areas were the focus, skin and respiratory diseases had received most attention (13.6% each; N= 3/22), followed by haematological and orthopaedic (9.1% each; N= 2/22), and finally neurologic and ophthalmologic diseases (4.5% each; N= 1/22). It is notable that publications had not targeted important clinical fields such as cardiovascular, gastroenterological and cancers other than blood diseases (Table 5).

**Table 5: Disease areas in clinical publications**

(Among the book chapters, the Gaucher disease has been considered both as an haematologic disease (Type 2) and as a neurologic disease (Types 2 and 3).)

	Number of articles N= 22	Number of books' chapters N= 1	Total N=23
General	10 45,5%	0 0%	10 43,5%
Haematological	2 9,1%	1 100%	3 13,0%
Neurologic	1 4,5%	1 100%	2 8,7%
Skin	3 13,6%	0 0%	3 13,0%
Respiratory	3 13,6%	0 0%	3 13,0%
Gastroenterological	0 0%	0 0%	0 0%

Orthopaedic	2 9,1%	0 0%	2 8,7%
Cancers (other than blood)	0 0%	0 0%	0 0%
Ophthalmologic	1 4,5%	0 0%	1 4,3%
Cardiovascular	0 0%	0 0%	0 0%
Total	22 100%	2 200%	23 100%

Furthermore, while “United Kingdom” was one of our selection criteria, first authors are from the UK in 40% (N= 20/50) of all the publications. The clinical and SHS areas are the main fields with UK first author’s affiliation when we consider all types of publications (clinical area (20%; N= 10/50) and SHS area (12%; N= 6/50)), or journals only (clinical (66.7%; N= 10/15) and SHS (20%; N= 3/15) journals)) (Table 6).

**Table 6: UK first author affiliation**

	Clinical	SHS	Economics	Public Health	Business	Total
UK first in journals	10/15 66,7%	3/15 20%	1/15 6,7%	1/15 6,7%	0/15 0%	15/50 30%
UK first in book chapters	0/2 0%	1/2 50%	0/2 0%	N/A	1/2 50%	2/50 4%
UK first in books	N/A	0/1 0%	N/A	N/A	1/1 100%	1/50 2%
UK first in thesis	N/A	2/2 100%	N/A	N/A	0 0%	2/50 4%
UK first in other publication	N/A	N/A	N/A	N/A	0/0 0%	0/50 0%
UK first author in all publications (N=50)	10/50 20%	6/50 12%	1/50 2%	1/50 2%	2/50 4%	20/50 40%

Reimbursement of RM is also considered by a wide range of different journals. Indeed, 83.7% (N= 31/37) appeared in separate journals across all fields, suggesting a very diffuse and emerging picture. Nevertheless, the public health and economics fields appeared as significant exceptions with 3/4 of public health articles published in the “Journal of Market Access and Policy”, 2/3 of economics journals’ publications published in the “Value in Health” journal (Table 7).

**Table 7: Publications in range of different journals**



	Clinical	SHS	Economics	Public Health	Business	Total
Publications in different journals	19/22 86,3%	8/8 100%	2/3 66,7%	2/4 50,0%	0/0 0%	31/37 83,7%

A wide spread of publishers was also evident. Four publishers shared 52% (N=26/50) of RM reimbursement publications, and Elsevier and universities covered the widest range of different fields (4): clinical, SHS, economics and public health for Elsevier, and clinical, SHS, economics and business for universities, suggesting a mix of commercial and non-profit commitment to the field. Most other publishers were specific to one or two fields.

Thus, it appears RM reimbursement publications are mainly in clinical journals although reimbursement might be considered primarily an SHS or Economics topic. This may be linked to the overall numeric domination of clinical publications compared to SHS or economics publications, or to the interest of medical practitioners and researchers in scenarios for clinical translation. While the question of RM reimbursement was often considered generally, where specific disease areas are targeted, it corresponded to those in which RM is closer to or already in the clinic: Skin and respiratory disease, haematological and orthopaedic and neurologic and ophthalmologic diseases. Finally, two journals (Journal of Market Access and Policy and Value in Health) and two publishers (Elsevier and Universities as a group) seem to be the most active on the topic of RM reimbursement.

### 3) Trade associations' positions on RM reimbursement issues

We now turn from the forms and disciplines with which reimbursement is being studied and debated to the actual content of the key debates and proposals. Thus, the third analysis is part of a study based on 43 semi-structured interviews of stakeholders from key institutions in the field of RM in the UK, conducted in 2015 and 2016: national bodies (5), service providers (3), consultancy companies/law academics (4), regulatory agencies/Institute (4), Innovation networks (organisations that promote relevant innovation) (4), trade organisations (4), funders (2), health professional organisations (4), research charities (10), other institutions (4). (Details of the organisations are available in Supplementary file 4). Interviews lasted around 1 hour, generally at the offices of the interviewees and covered both general questions on the interviewees' current perceptions of the RM field and of its prospects and specific questions modified according to each interviewee/institution.. Informed consent was obtained and interview transcripts were anonymised, and coded and analysed using Nvivo qualitative analysis software. The analysis of the whole set of interviews is the subject of another paper.

In this manuscript we target trade associations, as they were the category of stakeholders most involved and most critical of existing protocols on RM reimbursement. We supplemented the interviews with in-depth Internet searches, especially on the websites of the trade associations. We highlight key results and comments from four interviews in three associations. Although a small number, representatives of the associations held key senior positions and, of course, represent

the views of many member firms and other organisations. To preserve anonymity we identify the trade organisations/interviewees by a number.

All the trade associations considered reimbursement to be a current issue:

*“So I think we have the academic excellence, some significant infrastructure, a growing community on the positive side. What we don’t have is a route to reimbursement.”* (Trade organisation 2)

One trade association highlights the uncertainty of reimbursement decisions: unclear remits of relevant institutions in the context of multiple reimbursement pathways:

*“At the moment, we have some theoretical routes and we have a number of European companies that have gone bust trying to solve this problem.”* (Trade organisation 2)

Trade associations specifically highlight the contradictions or lack of collaboration between the National Institute for Health and Care Excellence (NICE) and National Health Service (NHS) England. Specific issues identified included: different criteria used by NICE and NHS England such as the gap between marketing authorisation and reimbursement decision; a perceived need for NICE and NHS England integration in an ‘holistic system’; tension between NICE and NHS England, although recognition that NICE Office for Market Access has been established to provide clarifications regarding procedures; alleged problems with NICE methodologies; NHS England’s specialised commissioning (i.e. many innovations competing for access to the specialised commissioning budget, NHSE not being seen as good at commercial access models); difficulties relating to the cost and choices to be made, long-term and uncertainty of evidence; routes to adoption in the clinic; the differences between devolved nations; difficulty of reaching a common product assessment at the European level; and the impact of (NICE) reimbursement decisions:

*“For things that go to NICE, whatever they are, that absolutely affects their fortune in the market and through the rest of their lifecycle. So the signal that NICE sends absolutely affects the commercial success of medicines and that will be true of regenerative medicines.”* (Trade Organisation 4)

Moreover, three out of four trade organisations expressed views on reimbursement methodologies for RM. One trade association considered NHSE methodologies had already changed but that NICE methodologies should be revised for RMPs. Indeed, three trade organisations explicitly said there is a need for change in reimbursement methodologies.

Regarding the possible establishment of a specific government supported fund for RM, one trade organisation was clearly in favour of it, while 2 others were not opposed to it. A fund for innovative medicines was seen as more acceptable than a disease- type fund such as the Cancer Drugs Fund [15], but it should be a ‘transition’ fund. They highlighted that the advantages of a specific fund for RM would be especially to provide flexibility. Moreover, as a budget is necessary to make a system change, the fund would be a powerful and potent mechanism for market access although it raised issues:

*“There’s no doubt that if you want to get something done and you want to make a system change, you create a ring-fenced budget. (...) So in terms of market access it’s (a specific fund is) a very powerful and potent mechanism, but it goes against the grain of travel of the system, which is not to have centralised budgets for things, but to have devolved responsibility and decision-making spread out across the system.”* (Trade organisation 4)

Finally, trade associations have made proposals for the reimbursement of RM based products. First, collaborations should be enhanced between marketing authorisation and reimbursement steps, that is, between regulatory agencies and reimbursement bodies. Indeed,

“A partnership approach (between developers and gatekeepers) has the potential to reduce the time and cost of development, while improving clinical relevance of studies and their assessment of cost-effectiveness. Improving public health through appropriate uptake of medicines at lower cost and improved cost-effectiveness, without any reduction in development standards or scrutiny, is an important incentive to develop new methodology. Real time database utilisation, new analytical methods and adaptive approaches can underpin this.” [16]

Second, one trade association emphasised that changes should occur at NHS England: a perceived need for direct producer engagement with NHS England, a key aspect being ‘good horizon scanning’ at NHS England, whilst approving the new clinically focused routes for reimbursement (i.e. Clinical Reference Groups). Third, one trade organisation highlighted a need for general systemic changes to achieve a healthcare service with a good way of both monitoring and assessing patient performance over time, and the need for industry to have a coherent business strategy. Fourth, two trade organisations underlined that a broader or specific view should be taken for RMPs such as a need for different thinking around the benefits models, especially where there is a curative effect. Fifth, one trade organisation has envisaged ‘adaptive pathways’ [17] as a solution for RM based products as they could take into account their specific issues, while another referred to risk- sharing or annual/stages payment models:

*“The key thing is there has to be recognition that the risk has to be shared between the company and the system. So it’s no good if the system says, ‘Okay, you’ll have to supply the medicine for free through this period and we’ll look at it again in two years.’ There needs to be more flexibility to say, ‘Okay, so maybe the medicine will be provided at a different in-market commercial price for this period,’ but then, if the data supports it, the price should go up. (...) and it’s only if we accept that that we’re properly accepting that value should be linked to price.”* (Trade organisation 4)

However, one trade organisation highlighted, as above, that these reimbursement models need connectivity between regulatory and HTA bodies, and between NICE and NHS England, early discussions with HTA bodies and a structured framework for data collection. Finally, one trade organisation welcomed the Japanese model for faster access to market and conditional reimbursement [18] although it recognised it needs to be tested.

Thus, beyond recognising reimbursement issues for RMPs, trade organisations generally have views on what are these issues and how they could be solved. Indeed, BIA and ABPI recognise these issues on their websites or positions papers, especially from 2015 [19,20,21,22,23,24], in collaboration together [25] and with other trade associations as well [26,27,28], following some earlier statements [29,30]. ABPI was represented on this topic at the 2015 conference of the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) [31].

The general views of the trade organisations could be summarised by this statement:

“Ultimately a major consideration is whether payors - especially the NHS in the UK - can afford to use the medicine. Biological medicines, especially advanced therapies like cell and gene therapies, have particularly high development and manufacture costs. But they may also provide healthcare benefits that ultimately save the NHS money down the line. There is a need for policymakers to consider short, versus long-term, trade-offs and to propose models for realistic reimbursement plans.” [28]

#### **4) Discussion**

In this section, we summarise and discuss the main results of the three studies:

The valuation of regenerative medicine involves a politics of stakeholder institutions and emerging policy discourse evident in the interview positions and publication profiles that we have presented. It could be considered that 2015 constituted a turning-point in that reimbursement and adoption in the NHS became a key issue in new national reports [32,33]. Moreover, the reimbursement of the first authorized Advanced Therapy Medicinal Product (ATMP), Chondrocelect in 2009, was turned down for reimbursement both in France and in the UK. In 2016, its marketing authorization holder, Tigenix NV, decided to withdraw its marketing authorization, as did Dendreon/Valeant for Provenge in 2015, for commercial reasons. Thus, the commercial viability of ATMP and RM products, as linked to the decisions of reimbursement by national bodies, became a key challenge. Indeed, “the reimbursement point is the keystone from which an allowable COGs [Cost of Goods] is determined by subtracting business costs.” [34]

These developments show the volatile environment in which valuation and reimbursement of RMPs is being debated. We have shown that it has been a growing topic of focused publications between 2015 and 2016, the vast majority of which appear in very disparate avenues or ‘spaces’ geared to various disciplinary audiences and interested parties. Nevertheless, clinical and especially generalist medical journals were shown to be dominating, and at least two specialist journals have appeared recently, which are likely to see more RMP reimbursement contributions.

Many of the reimbursement challenges are not specific to RMPs, because other fields such as orphan drugs can also have high up- front costs [35,36]. However, we maintain that some kinds of RMPs raise specific challenges, such as gene therapies when they are curative [37]. We have shown that risk- sharing specifically is far less discussed than reimbursement generally. This result accords with risk- sharing schemes being just one strategy for dealing with RM reimbursement, albeit a widely debated one. Indeed,

these schemes can be considered as one way of addressing the uncertainties regarding the alternative approaches to the valuation of RM between different actors, especially the NHS and the producer/manufacturer.

Reimbursement and risk- sharing are distinct issues for RM, although there is an overlap with the same issues for orphan drugs. RMPs can be medicinal products, especially ATMPs. For instance, Holoclar, the first stem cell- based medicinal product approved for use in the EU, is both an ATMP and an orphan medicinal product, and as such benefits from the incentives of both regulatory frameworks [38]. More globally, among the eight ATMPs authorised on the EU market to date, four are orphan drugs. As those cases show, orphan drugs and RM based products often share the two main features of high cost and uncertainties around evidence and value [39,40]. However, these same uncertainties are also seen in the weak long- term evidence for RMPs that are not orphan drugs. Even though there was an increase in using risk-sharing schemes in Europe generally [41] and they have been considered suitable for orphan drugs [42], there should be further exploration of whether such schemes might be more applicable to orphan drugs than RM products, as our findings imply. Such considerations are important to the political design of the markets and health system adoption of different subsectors of RM and related enterprise.

We showed in the first study the UK's position in the RM reimbursement publication landscape. Those results are in keeping with several reports in the field of RM evidencing different countries' positions addressing RM challenges broadly:

“The UK needs to be ambitious and act quickly to get ahead. The USA, Canada and Japan are particularly active in this space and, although the UK is preeminent in Europe; Germany, Italy, France and Spain, in particular are rapidly reviewing how they can also capture these investments.” [43]

Regarding the distribution of RM tissue engineering firms and research institutes:

“When we look at the geographic distribution of tissue engineering firms and research institutes, the U.S. with 52% leads the market followed by Germany (21%), Japan (16%), the UK (7%), and Sweden (4%).” [44]

This pattern has been established for some time across the biopharmaceutical sector said to reflect ‘longstanding problems: limited venture capital finance, a fragmented patent system, and relatively weak relations between academia and industry.’ [45]. Our publications analysis and interviews suggest that the UK's position in the emerging RM reimbursement landscape is similar.

Clearly, trade organisations have been very involved in RMPs reimbursement debates, as one would expect. Indeed, the industry is the most critical of RM valuation issues. Industry generally will not develop medicines lacking likely wide reimbursement and thus uncertain return on investment. Trade organisations consider more flexibility is needed, notably regarding NICE methodologies for assessment. In the context of limited budgets for healthcare, we showed in our interview and internet study that several key trade organisations argue that new flexible routes for reimbursement are needed to ensure patient access to the latest medical advances, including RMPs.

Beyond acceptance for risk- sharing schemes, while highlighting their limits, trade organisations emphasised the need for more collaboration between key stakeholders as a main solution to reimbursement issues. Some measures have been taken toward this objective, such as promotion of early contact with regulators and HTA bodies notably through the NICE Office for Market Access. The latter's objectives include defining acceptable evidences in a context of uncertainty with a curative treatment, and supporting navigation between the different gatekeepers. This is seen as particularly necessary given the challenge of an "increase in demand for 'real world' evidence by HTA, payers and regulators", i.e. their "growing interest in relative effectiveness" [46].

## **5) Conclusion**

We conclude that the policy and institutional landscape of reimbursement studies in RM is a highly variegated one and in its infancy. The two publications studies gave details on the amount of activities going on, the potential gap in the field, and signs of both general and niche trends. The volume of publications is growing, as researchers and analysts in a wide variety of disciplines and types of organisation start to grapple with reimbursement challenges. The interviews study highlights trade associations as closely engaged with debating at a high level the possible reimbursement scenarios for RM, and pointing to ways in which current technology assessment and healthcare infrastructures could be improved to favour RM enterprise. The analysis that we have provided is particularly relevant to the stakeholders involved in policy making in RM, and industry and academia. It offers a picture of the emerging landscape of RM reimbursement actors and issues that can inform the various stakeholders' participation in its future analysis, potential, and development.

## **Summary Points**

- Reimbursement of RM based products has been a growing topic of publications between 2015 and 2016, independently from orphan drugs.
- Risk- sharing schemes are only one strategy for dealing with RM reimbursement, albeit a widely debated one.
- Reimbursement and risk- sharing are distinct issues for RM, although there is an overlap with the same issues for orphan drugs.
- The UK's position in the RM reimbursement publication landscape is in keeping with several reports on the global dynamics of RM.
- Trade organisations have been very involved on RM based products reimbursement issues.
- Trade organisations have detailed views on reimbursement issues for RM especially the high cost versus the uncertainty regarding long- term evidence.
- Trade organisations have various proposals to solve RM reimbursement issues, emphasising a need for more collaboration between several key national-level actors.

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